REMARKS

Claims 2-19, 22-37, 39 and 40 are pending in the present Application, with claims 3, 5-15, 17, 19, 23-37 and 39 withdrawn from consideration.

Claim 22 has been amended to correct the preamble to recite "the compound, " as claim 22 depends from claim 40. As this amendment is directed only to matters of form, and does not alter the scope of the claim, entry is respectfully requested.

No other claims have been added, or cancelled, leaving claims 2-19, 22-37, 39, and 40 for active consideration.

Reconsideration and allowance of the claims are respectfully requested in view of the following remarks.

Claim Rejections Under 35 U.S.C. § 103(a)

Claims 2, 4, 16, 18, 22, and 40 stand rejected under 35 U.S.C. § 103(a), as allegedly unpatentable over U.S. Patent No. 6,638,502 to Li et al. (hereinafter "Li"), in view of U.S. Patent No. 5,733,548 to Restifo et al (hereinafter "Restifo"). Applicants respectfully traverse this rejection.

The pending claims are directed to a compound comprising a recombinant nucleic acid encoding an antiangiogenic protein operatively linked to an adenovirus E19 signal sequence inserted within a viral nucleic acid. The recombinant nucleic acid can be packaged in a virus particle, and expression of the recombinant nucleic acid encoding the antiangiogenic protein results in production of the antiangiogenic protein. The antiangiogenic protein targets endothelial cells such that systemic delivery of the compound results in increasing circulating levels of the antiangiogenic protein and inhibition of tumor growth. Applicants have shown unexpectedly that by operatively linking an antiangiogenic protein to the adenovirus E19 signal sequence, circulating levels of antiangiogenic protein can be detected upon systemic administration. Further, these compositions are particularly useful for treating tumors upon such systemic delivery.

Restifo discloses that the E3/19K signal sequence is a sequence that "targets . . . proteins to the endoplasmic reticulum." (Col. 4, ll. 11-24) There is no teaching or suggestion in Restifo that the signal sequence has any function other than targeting proteins to the ER. In Restifo, the E3/19K signal sequence is covalently linked to 5 to 1000 amino acid-long peptides to form a

chimeric protein containing the signal sequence. (Col. 4, ll. 32-40) The peptides are derived from "a tumor cell, virus, bacteria, or parasite, or it may be associated with an autoimmune disease." (Col. 4, ll. 38-40) The chimeric polypeptides are delivered to the ER by the signal sequence, where they associate with class I MHC molecules to form a peptide/class I MHC molecule complex that is then transported to the cell surface to elicit a response against the peptide. (Col. 2, ll. 4-17) The assays employed in Restifo are ^{51}Cr assays for T cell activity; the peptides themselves are not directly detected. It appears that the antigenic peptides/class I MHC complexes are bound to the cell, and not secreted into circulation.

Li discloses adenovirus-directed intratumoral delivery of angiogenesis agonists such as the amino-terminal fragment of urokinase (ATF). (Abstract) Li teaches that signal sequences can be used as "trafficking" sequences. Li specifically discloses the use of the uPA signal sequence and the plasminogen signal sequence.

For an obviousness rejection to be proper, the Examiner must meet the burden of establishing that all elements of the invention are disclosed in the prior art; that the prior art relied upon, or knowledge generally available in the art at the time of the invention, must provide some suggestion or incentive that would have motivated the skilled artisan to modify a reference or combined references. *In re Fine*, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). "A patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741 (2007). To find obviousness, the Examiner must "identify a reason that would have prompted a person of ordinary skill in the art in the relevant field to combine the elements in the way the claimed new invention does." *Id.*

In the Final Office Action dated September 16, 2009, the Examiner makes eight points in response to Applicants' arguments filed in the response dated February 17, 2009. Applicants respond to each point in turn below.

Point 1: The results of the application are surprising in light of the teachings of Gabathuler et al. regarding the E3/19K protein.

In the September 16, 2009 Office Action, the Examiner states that "Gabathuler et al. teaches that the E3/19K protein has an ER retention signal at the carboxy terminus." (September

16, 2009 Office Action, p. 3) The Examiner concludes that "the function of such a protein in nature to sequester MHC molecules in the secretory pathway (emphasis added) does not mitigate against the rejection in light of the prior art teachings made of record." (Id. at 4)

Upon a careful reading of Gabathuler et al., Applicants note that the native E3/19K protein of adenovirus has an N-terminal cleavable signal sequence that directs the protein into the endoplasmic reticulum (ER), and a carboxy terminal endoplasmic reticulum retention signal that maintains the protein as a resident ER protein. Applicants emphasize that Gabathuler et al. provides no teaching or suggestion that the E3/19K signal sequence functions to target the E3/19K protein to the secretory pathway as alleged by the Examiner, only that it directs the E3/19K protein into the endoplasmic reticulum after synthesis of the protein by membrane-bound ribosomes. Once the E3/19K protein is in the endoplasmic reticulum, it is bound to class I MHC (HLA in humans) antigens, and retained in the ER by the retention signal. Gabathuler et al. show that E3/19K polypeptides with defective retention signals bind MHC class I antigens in the ER and are then transported to the cell surface. It is, in fact, the HLA antigens that Gabathuler et al. localizes in their assays, and not the E3/19K protein itself. There is nothing in Gabathuler et al. that suggests in any way that the E3/19K signal sequence targets the E3/19K proteins with a defective ER retention signal to the secretory pathway, only that the retention signal-defective proteins bind class I MHC antigens and reach the cell surface. As explained in more detail under point 2, binding to class I MHC antigens provides a pathway for entry of polypeptides into the secretory pathway. It appears from p. 1803, col. 2, of Gabathuler et al. that the bound class I MHC antigens are responsible for the cell surface location of the E3/19K protein in the absence of the retention signal. Thus, there is no indication in Gabathuler et al. that the E3/19K signal sequence does anything more than target the E3/19K peptide to the ER. Further, given that the E3/19K protein has a signal sequence for translocation to the ER and an ER retention sequence, there appears to be no functional requirement for a signal sequence that targets the E3/19K protein to the secretory pathway.

There are two independent steps involved in a protein entering the secretory pathway: first entering the ER, and second, once in the ER, the proteins that are to be secreted are moved to the Golgi for secretion. Gabathuler et al. only teaches the first half of the process, transport to the ER. There is nothing in Gabathuler et al. to suggest that the E3/K19 signal sequence has any role

other than delivering peptides to class I MHC antigens in the ER. Thus, the results demonstrated by the Applicants that the E3/19K signal sequence can direct a polypeptide that does not bind class I MHC antigens to the secretory pathway is surprising in view of Gabathuler et al. Gabathuler et al. provide no teaching or suggestion of any function of the E3/19K signal sequence other than transporting cargo polypeptides to the ER for association with class I MHC antigens in the ER. Applicants maintain the results described in the application are indeed surprising in view of Gabathuler et al.

Point 2: Restifo et al. involves the targeting of a peptide to the ER in order to associate it with MHC.

In making the rejection, the Examiner states that "peptides associated with MHC molecules are broadly considered 'secreted,' despite applicants assertions and protests to the contrary." (September 16, 2009 Office Action, p. 4)

Applicants agree with the Examiner that ultimately the peptides associated with MHC molecules are "secreted," at least to the cell surface. However, there is no teaching or suggestion in Restifo that it is the E3/19K signal sequence that directs peptides associated with MHC molecules to the cell surface. According to Restifo, the E3/19K signal sequence transports covalent linked immunogenic peptides to the endoplasmic reticulum. This is consistent with Gabathuler et al. as discussed above. In the endoplasmic reticulum, the immunogenic peptides associate with class I MHC molecules to form a class I MHC/peptide complex. Once the peptide is loaded onto the MHC class I molecule, it leaves the ER through the secretory pathway to reach the cell surface. This mechanism is consistent with Janeway, cited by the Examiner in the April 8, 2009 office action.

Thus, when immunogenic peptides in Restifo enter the endoplasmic reticulum, it would be counterproductive for them to immediately enter the secretory pathway, as they must first associate with class I MHC molecules. It is important for the peptides to form a class I MHC/peptide complex that then leaves the ER through the secretory pathway. It is particularly relevant that the assays presented in Restifo are T cell response assays, requiring the production of a class I MHC/peptide complex. Nowhere does Restifo directly examine the immunogenic peptides. There is no teaching or suggestion in Restifo that the immunogenic peptides with the

E3/19K signal sequence could ever enter the secretory pathway without bound class I MHC molecules. There is no teaching or suggestion that the E3/19K signal sequence directs secretion, only that it directs entry into the ER.

In sum, the constructs of Restifo have a completely different purpose than the presently claimed constructs, and there is no teaching or suggestion in Restifo that the E3/19K signal sequence could direct an attached peptide to the secretory pathway. In fact, if such a mechanism were present, it could impede interaction of the peptides with class I MHC molecules and ultimately reduce the desired T cell response. One of skill in the art, based on the teachings of Restifo and as further evidenced by Gabathuler et al., would only select the E3/19K signal sequence to attach to peptides with the goal of entry into the ER and complex formation with class I MHC molecules.

Again, the Examiner is directed to the Rule 1.132 Declaration of Dr. Renata Pasqualini, filed with the December 17, 2007 Response to Office Action. In the Declaration, Dr. Pasqualini stated: "people of skill in the cancer therapy field did not view Restifo et al. as providing a reasonable expectation that an adenoviral E3/19K signal sequence could drive expression of an antiangiogenic protein that targets endothelial cells, and results in increased circulating levels of the antiangiogenic protein." (p. 2) In the Office Action dated February 8, 2008, the Examiner dismissed the comments of Dr. Pasqualini noting that "opinion evidence on the ultimate legal issue is not persuasive. See MPEP § 716.01(III)." The Examiner is directed to the full text of the cited MPEP section as follows:

> While an opinion as to a legal conclusion is not entitled to any weight, the underlying basis for the opinion may be persuasive. *In re Chilowsky*, 306 F.2d 908, 134 USPQ 515 (CCPA 1962) (expert opinion that an application meets the requirements of 35 U.S.C. 112 is not entitled to any weight; however, facts supporting a basis for deciding that the specification complies with 35 U.S.C. 112 are entitled to some weight); *In re Lindell*, 385 F.2d 453, 155 USPQ 521 (CCPA 1967) (Although an affiant's or declarant's opinion on the ultimate legal issue is not evidence in the case, "some weight ought to be given to a persuasively supported statement of one skilled in the art on what was not obvious to him." 385 F.2d at 456, 155 USPQ at 524 (emphasis in original)).

Thus, while opinions as to legal conclusions may be given little or no weight, opinions as to facts that underlie the legal conclusions are entitled to weight. Here, Dr. Pasqualini's conclusions are directed to facts regarding how those of skill in the art at the time of the invention

would have interpreted the teachings of Restifo. In particular, Dr. Pasqualini's conclusions are based on her understanding that the teaching of Restifo is limited to the use of the E3/19K signal sequence for expressing small immunogenic peptides, and that one of ordinary skill in the art (such as herself) would not look to Restifo for signal sequences for antiangiogenic sequences. Dr. Pasqualini bases her conclusion that there is no expectation of success because one of ordinary skill in the art would not look to Restifo to combine with Li.

In sum, targeting of peptides to class I MHC molecules as taught in Restifo differs completely from the claimed constructs in which the signal sequence is attached to an antiangiogenic protein.

Point 3: The art does not hint that proteins attached to the E3/19K signal sequence would be secreted.

In making the rejection, the Examiner states that "this statement is false on its face" and "the very purpose of signal sequences is to direct proteins to the secretory pathway." (September 16, 2009 Office Action, p. 4) Applicants disagree.

There is nothing in the cited references that teaches or suggests that the E3/19K signal sequence is directly responsible for **both** direction of proteins into the ER **and** moving of the proteins into the secretory pathway. Applicants maintain that the art does not hint that proteins attached to the E3/19K signal sequence would be secreted without binding to an additional component, namely class I MHC molecules. The Examiner is again directed to Janeway, cited in the April 8, 2009 Advisory Action. The art only fairly suggests that the E3/19K signal sequence directs proteins into the ER. Restifo and Gabathuler et al. in fact suggest that upon entry into the cell, the E3/19K polypeptide or immunogenic peptides linked to the E3/19Kare bound by HLA or class I MHC molecules prior to cell surface expression. Thus, there is no teaching in the cited references that the E3/19K signal sequence would be useful to direct **both** direction of proteins into the ER **and** moving of the proteins into the secretory pathway. In fact, given that the natural cargo of the E3/19K signal sequence must interact with class I MHC molecule, such an activity would be contrary to the purpose of the E3/19K signal sequence.

It is known in the art that signal sequences have a variety of roles in translocation of polypeptides. As defined in Li, a signal sequence broadly "directs the host cell to translocate the

polypeptide." However, the particular role that a given signal sequence plays in translocation is as varied as the individual sequences themselves. The Examiner appears to have taken the position here that E3/19K signal sequence directs a given polypeptide to both the endoplasmic reticulum and subsequently to the Golgi bodies, based only on the teaching in Restifo that the E3/19K signal sequence plays a role in a part of the secretory pathway. However, there is no requirement for the same signal sequence that directs the attached polypeptide to the endoplasmic reticulum to direct the polypeptide into the secretory pathway. It is equally possible, if not probable, that a signal sequence that directs an attached polypeptide to the endoplasmic reticulum is not the same as any signal sequence that directs the polypeptide to the Golgi bodies. Neither Restifo nor Gabathuler et al. state that the E3/19K signal sequence directs molecules into the secretory pathway, only that it directs them to the ER for interaction with Class I MHC molecules. The broad disclosure of signal sequences in Li therefore does not imply any requirement for direction of proteins to the secretory pathway.

In sum, Applicants maintain that there is nothing in the cited prior art that suggests that the E3/19K signal sequence directs attached polypeptides to the secretory pathway once they enter the ERl; rather it directs them to the ER for association with class I MHC molecules.

Point 4: Li teaches that the signal sequence is not the E3/19K signal sequence.

The Examiner has oversimplified the Applicants' statements in the February 17, 2009 response. Applicants maintain that Li teaches signal sequences broadly, and specifically the signal sequence from angiostatin; Li do not teach the E3/19K signal sequence.

What Li teaches is signal sequences in a broad sense as translocation sequences. The signal sequences exemplified in Li are the uPA signal sequence or the plasminogen signal sequence. As explained in Li at Col. 30, line 61 to Col. 61, line 8, secretion of angiostatin was required to give the desired arrest in proliferation in vitro. Thus, it would appear that the constructs exemplified in Li have signal sequences that direct peptides to the secretory pathway, although this is not explicitly stated.

Applicants maintain that when reading Restifo and Li as a whole, one would not select the E3/19K signal sequence disclosed in Restifo to express antiangiogenic peptides as disclosed in Li. There is no teaching or suggestion in either reference that the E3/19K signal sequence directs

attached polypeptides to the Golgi bodies, that is, to the secretory pathway. Further, as explained previously, there is no teaching or suggestion that the E3/19K signal sequence can be used to deliver heterologous peptides longer than the immunogenic peptides of Restifo. The immunogenic peptides of Restifo are completely different from the antiangiogenic polypeptides of Li and are expressed for different purposes. Further, as will be explained below, the use of the E3/19K signal sequence with an antiangiogenic polypeptide is a nonobvious selection of invention from the multitude of signal sequences in the literature.

In sum, Li does not specifically teach the E3/19K signal sequence.

Point 5: The present rejection is based on the assumption that all signal sequences are the same, which is contradicted by the prior art

In making the rejection, the Examiner states that "a review of the prosecution of this application reveals no such statement by the Examiner." (September 16, 2009 Office Action, p. 5) Applicants note that in the February 22, 2006 Office Action, for example, the Examiner stated that "Li et al. teaches the interchangeability of different signal sequences to secrete the desired antiangiogenic protein." (p. 6) Applicants can find no such explicit teaching in Li. What Li does is define signal sequences broadly and then employ two different signal sequences. In the February 8, 2008 Office Action, the Examiner appears to rely on Martiglio for the assertion that signal sequences can be interchanged between peptides and organisms. (pp. 4-5) In fact, while Martiglio does state that signal sequences can be interchanged (p. 410), the discussion immediately following, and indeed the rest of the article, contains an extensive discussion of the differentiated view of signal sequences as discriminating between different target pathways, mediating translocation, allowing variable membrane translocation, and even having further function after cleavage. In the conclusion, Martiglio states that "The high degree of sequence and length variation of signal sequences, which has long been a puzzle, is now revealed as the basis for an amazing complexity and versatility of signal sequence function." (p. 415, col. 1) Thus, while there is clearly some interchangeability between signal sequences, it is also true that they are not equivalent and that it would require a great deal of experimentation and creativity to select a particular signal sequence for a specific application, in the present case, secretion of antiangiogenic polypeptides.

The Examiner also suggests that Hegde et al. supports the predictability of the function and action of signal sequences because Hegde et al. does not refute the Examiner's assertion of "the predictability of using the instantly claimed sequence, which is to be used in the very organism it has evolved to be effective in (humans)." (September 16, 2009 Office Action, p. 5) The Examiner has in fact oversimplified Hegde et al. as well as Martiglio et al. Simply because an adenovirus signal sequence has "evolved to be functional in human cells" does not mitigate the fact that there is no suggestion in the references that the E3/19K signal sequence would be effective in the secretion of an antiangiogenic polypeptide. Like Martiglio et al., Hegde et al. conclude that "The challenge in the future will be not only to continue uncovering the diversity in signal sequence functionality, but also to determine whether and how this diversity has been exploited to impart greater control on protein biogenesis to suit constantly changing cellular needs." (p. 569, Col. 2) Given the diverse array of signal sequences and their functionality, the question is rather what would motivate one to select a particular signal sequence for expression of a particular class of proteins, in this case antiangiogenic proteins.

The prior art teaches a vast number of signal sequences that have diverse functions, so how would one of skill in the art choose a particular signal sequence for a particular application? Particularly relevant is *In re Kubin*, case number 08-1184, decision dated April 3, 2009. The Federal Circuit cited *In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988), stating:

> In such circumstances, where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness. The inverse of this proposition is succinctly encapsulated by the Supreme Court's statement in KSR that where a skilled artisan merely pursues "known options" from a "finite number of identified, predictable solutions," obviousness under § 103 arises. 550 U.S. at 421.

In the present case, given the number of signal sequences of varying functionalities in the prior art, there is nothing in the prior art that would have led one to specifically select the E3/19K signal sequence of Restifo. The Examiner has used improper hindsight to select from all of the possible signal sequences the signal sequence from Restifo. Li defines signal sequences broadly, and such a broad definition actually supports the Applicants' contention that selecting the E3/19K signal sequence is like throwing darts at the dartboard of possible signal sequences. Given the complexity and versatility of signal sequences as described in Martiglio et al. and Hegde et al.,

there is simply nothing in the prior art that would direct one to the E3/19K signal sequence for use with an antiangiogenic protein as the Applicants have done.

The Supreme Court has recently reaffirmed the principle that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the art. . . . This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *KSR Int'l. Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007). The Court further stated that "[r]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *Id.* (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)). However, "the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* And the Court expressly encouraged the use of common sense in such analysis. *Id.* Finally, the Court agreed that the teaching-suggestion-motivation test ("TSM test") captured a helpful insight to prevent hindsight bias, but the Court held that "[h]elpful insights, however, need not become rigid and mandatory formulas; and when it is so applied, the TSM test is incompatible with our precedents." *Id.*

In the present case, the Examiner has provided no basis for selecting the E3/19K signal sequence other than that Restifo allegedly teaches that it is a well-known secretion signal and that Li broadly teaches the use of signal sequences. (See, e.g., February 22, 2006 Office Action) First, as has been explained in great detail above, Restifo does not teach that the E3/19K signal sequence is a secretion signal, only that it directs peptides to the ER. Second, given the diversity of signal sequences, the Examiner has provided no explanation as to what would direct one of skill in the art to this particular signal sequence. It is of note that Li does not specify that signal sequences that direct secretion are preferred, only that signal sequences direct translocation. Again, the Applicants' selection of the E3/19K signal sequence and an antiangiogenic protein is a nonobvious selection from the breadth of signal sequences in the prior art. Given the breadth of Li and the art regarding signal sequences and their functions, there is simply nothing in the art that would direct one of skill in the art to select the E3/19K signal sequence.

In sum, Applicants submit that the genus of signal sequences is broad and heterogeneous, and there is nothing in the prior art that would have led one to select the E3/19K signal sequence for use with antiangiogenic polypeptides. The Applicants' claims are a nonobvious selection of invention of the prior art of signal sequences and potential cargo polypeptides.

Point 6: Neither Restifo nor Li teach that the E3/19K signal sequence will predictably express a secreted form of an antiangiogenesis protein commensurate in scope with the claims.

In making the rejection, the Examiner states that "this is, again, a statement of opinion that is false on its face and completely ignores the facts and evidence found in the teachings of Restifo and Li et al." (September 16, 2009 Office Action, p. 5) The Examiner further asserts that "[t]he E19 signal sequence, again, was used to direct expression and secretion of given peptides." (*Id.*)

Consistently, the Examiner has alleged that one would use the E3/19K signal sequence to direct secretion. Yet, there is nothing in either Restifo or Gabathuler et al. that would indicate that the E3/19K signal sequence does anything more than direct proteins to the ER. There is nothing in the cited references that suggests that the E3/19K signal sequence directs secretion once the protein or peptide is bound to HLA or class I MHC molecules.

The Examiner further alleges that "there is nothing surprising about a known antiangiogenic protein reducing tumor growth when administered to a tumor or an animal having a tumor." (September 16, 2009 Office Action, p. 5)

While it is true that an antiangiogenic protein would be expected to reduce tumor growth when delivered to a tumor, it is unexpected that inclusion of a E3/19K signal sequence would allow the antiangiogenic peptide into circulation to reduce tumor growth. As shown in the present Specification in Example III, upon intravenous, intraperitoneal, intrasplenic or intranasal delivery, the endostatin plasma levels were all higher than control. Thus, the inventors have shown that <u>systemic</u> rather than <u>tumor-directed</u> therapy such as that taught in Li can produce therapeutic circulating levels of endostatin in a mouse model. Neither Restifo nor Li demonstrates that the E3/19K signal sequence can produce circulating levels of any protein, let alone an antiangiogenic protein.

In sum, the cited prior art does not teach that the E3/19K signal sequence will predictably express a secreted form of an antiangiogenesis protein commensurate in scope with the claims.

Point 7: Nothing in the prior art suggests arriving at a composition that reduces tumor growth when administered systemically.

In making the rejection, the Examiner states that "nothing in [Applicants'] arguments details what exactly the structural limitation imposed by this intended use might be." (September 16, 2009 Office Action, p. 6)

The Examiner appears to confuse functional language with structural language. From MPEP 2173.05(g):

> A functional limitation must be evaluated and considered, just like any other limitation of the claim, for what it fairly conveys to a person of ordinary skill in the pertinent art in the context in which it is used. A functional limitation is often used in association with an element, ingredient, or step of a process to define a particular capability or purpose that is served by the recited element, ingredient or step. In *Innova/Pure Water Inc. v. Safari Water Filtration Sys. Inc.*, 381 F.3d 1111, 1117-20, 72 USPQ2d 1001, 1006-08 (Fed. Cir. 2004), the court noted that the claim term "operatively connected" is "a general descriptive claim term frequently used in patent drafting to reflect a functional relationship between claimed components," that is, the term "means the claimed components must be connected in a way to perform a designated function." "In the absence of modifiers, general descriptive terms are typically construed as having their full meaning." *Id.* at 1118, 72 USPQ2d at 1006. In the patent claim at issue, "subject to any clear and unmistakable disavowal of claim scope, the term 'operatively connected' takes the full breath of its ordinary meaning, i.e., 'said tube [is] operatively connected to said cap' when the tube and cap are arranged in a manner capable of performing the function of filtering." *Id.* at 1120, 72 USPQ2d at 1008. It was held that the limitation used to define a radical on a chemical compound as "incapable of forming a dye with said oxidizing developing agent" although functional, was perfectly acceptable because it set definite boundaries on the patent protection sought. *In re Barr*, 444 F.2d 588, 170 USPQ 33 (CCPA 1971).

In the present case, "systemic delivery results in increased circulating levels of the antiangiogenic protein and inhibition of tumor growth" sets definite boundaries on the claimed composition. This limitation restricts the claim to those compositions that meet the claimed limitation upon systemic delivery, readily testable in, for example, a mouse model as disclosed in Applicants' specification in Example III. Applicants maintain that if this functional limitation is given its proper weight, Restifo and Li do not render such a composition obvious. There is no demonstration in Restifo and Li. et al. of any composition wherein "systemic delivery results in increased circulating levels of the antiangiogenic protein and inhibition of tumor growth."

In sum, the prior art does not suggest a composition wherein "systemic delivery results in increased circulating levels of the antiangiogenic protein and inhibition of tumor growth" as presently claimed.

Point 8: Griscelli et al. does not remedy the deficiencies of Restifo and Li.

Applicants maintain that Griscelli et al. does not remedy the deficiencies of Restifo and Li. Griscelli et al. teaches an adenoviral vector that expresses amino acids 1-333 from human plasminogen linked to the plasminogen signal sequence. The results obtained with this vector have no relevance to the likelihood of success of the presently claimed compounds for at least two reasons.

First, the Griscelli et al. system is a homogeneous system, that is, a plasminogen signal sequence operatively linked to a plasminogen fragment. The presently claimed construct is a heterologous construct, an E3/19K signal sequence and an antiangiogenic protein. The homogeneous construct does not provide an expectation of success for a heterogeneous construct.

Second, the results obtained with a plasminogen signal sequence are irrelevant to any result with an E3/19K signal sequence. These are completely different signal sequences and are not expected to be functionally equivalent based on the teachings of Martiglio et al. and Hegde et al. The success of systemic administration with a plasminogen signal sequence is in no way predictive a result with the E3/19K signal sequence, a completely unrelated sequence. There is simply no suggestion in any of the references cited by the Examiner that the E3/19K signal sequence operatively linked to an antiangiogenic protein could increase circulating levels of the antiangiogenic protein and provide the ability to treat tumors via systemic delivery.

In sum, Griscelli et al. does not make up for the deficiencies of Restifo and Li.

Summary

Applicants maintain that the combination of Restifo and Li. fails to render the present claims obvious at least because these references do not render obvious the selection of the E3/19K signal sequence to direct secretion of antiangiogenic proteins and do not provide any

expectation of success that such polypeptides can be secreted into the circulation at therapeutic levels.

Reconsideration and withdrawal of this rejection are respectfully requested.

If there are any additional charges with respect to this Amendment or otherwise, please charge them to Deposit Account No. 06-1130.

Respectfully submitted,

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